Contrast-Enhanced US in Pediatric Crohn’s Disease

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Disclosures

- Inflammatory bowel disease-related research funding from:
  - Siemens Medical Solutions USA
  - Bracco Diagnostics

- Will discuss non-FDA-approved use of microbubble contrast agents
Objectives

• Discuss advantages and disadvantages of contrast-enhanced US (CEUS) for assessment of pediatric Crohn’s disease (CD)

• Review recent literature regarding CEUS use in CD

• Briefly present my recent research experience using microbubble contrast agents in CD animal model as well as U.S. FDA Investigational New Drug (IND) process
Crohn’s disease (CD) = relapsing, remitting inflammatory condition affecting pediatric and adult GI tract

- 20-30% cases diagnosed during childhood/adolescence
  - Teenagers most often affected segment of pediatric population

- Increasing CD incidence in children
  - Doubled in recent 10-year period
Pediatric Crohn’s Disease

- Disease flares and complications common → repetitive imaging

- How do we image CD in U.S.?
  1. Suspected IBD (presence, extent, activity?)
     - MR enterography, CT entrography (CTE) >>> US
  2. Known IBD – worsening symptoms/complication?
     - CTE, MRE, ?US/CEUS
  3. Known IBD – “biomarker” for disease activity
     - MRE, CTE, ?US/CEUS
CEUS in Crohn’s Disease: a Primer

- Requires peripheral IV microbubble contrast agent injection
- 3 agents approved in U.S. – adult echo indications
  - Optison (perflutren protein-type A microspheres; GE Healthcare)
  - Definity (perflutren lipid microspheres; Lantheus)
  - Lumason (sulfur hexafluoride microbubble; Bracco)
- Allows real-time assessment of intestinal perfusion
  (contrast material wash-in & wash-out)
- Increasing body of research showing ability to depict small bowel CD inflammatory activity
CEUS in Action!

CEUS in Pediatric CD – Why Now?

1. Improved image quality (hardware/software)
   • Better transducers
   • Better CEUS image processing algorithms

2. More cost-effective vs. CTE/MRE?
   • Cheaper exam
   • No need for sedation/GA

3. NONIONIZING

4. Quantitative potential
Ionizing Radiation – Why the Concern?

• CD patients often exposed to repetitive ionizing imaging

• Radiation exposure more harmful in children?
  – Longer lifespans
  – Increased radiosensitivity (cells still dividing)

• Population at risk
  – Nature of the disease (e.g., adenocarcinomas)
  – Cancer-predisposing medications (e.g., lymphomas)

Brenner DJ. *Gut* 2008; 57:1489-1490
CEUS Advantages vs. CT/CTE: Disease Activity Assessment

1. NONIONIZING

2. Superior contrast resolution

3. Allows real-time assessment of bowel wall enhancement – QUANTITATIVE

4. Lower cost – “bang for buck”

5. Parent at bedside

6. Portability (GI clinic?)

7. Lower contrast agent adverse reaction rate?
Contrast Resolution in Action

CTE  MRE  CEUS (rat)
CEUS Disadvantages vs. CT/CTE: Disease Activity Assessment

1. Limited availability
   - Radiologist/gastroenterologist comfort
   - FDA issues ("off-label")

2. Relatively small FOV
   - Survey bowel with gray-scale & Doppler
   - Perform CEUS on most abnormal bowel segments (>1 injection?)
CEUS Advantages vs. MRE: Disease Activity Assessment

1. Lower cost – “bang for buck”
2. No sedation/GA requirement
3. Parent at bedside
4. Portability (GI clinic?)
5. Lower contrast adverse reaction rate?
CEUS Disadvantages vs. MRE: Disease Activity Assessment

1. Limited availability
   - Radiologist/gastroenterologist comfort
   - FDA issues (gadolinium “off-label”, too)

2. Relatively small FOV
   - Survey bowel with gray-scale & Doppler US
   - Perform CEUS on most abnormal bowel segments (>1 injection?)
CEUS vs. Doppler US in CD

- Subjective/objective Doppler signal correlates with activity
  - Numerous studies, mostly adults
- Difficult to quantify
  - Color/vessel density?
- No “number” to follow vs. time
CEUS: Quantitative Biomarker

Bolus model parameters

- Fit: Perfusion model
- Lin: Linearized signal
- PE: Peak Enhancement
- WiAUC: Area Under the Curve (Wash-in)
- RT: Rise Time
- mTII: mean Transit Time (local)
- TTP: Time To Peak
- WiR: Wash-in Rate
- WiPI: Wash-in Perfusion Index (WiAUC/RT)
- WoAUC: Wash-out AUC
- WiWoAUC: Wash-in and Wash-out AUC
- FT: Fall Time
- WoR: Wash-out Rate

Wash-in Rate

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Selected Recent CEUS Publications in CD (2012 – present)
Pubmed

- 19 publications
  - 2 meeting abstracts
  - 1 meta-analysis
  - 0 in children
• 54 consecutive adults, endoscopically confirmed TI CD
• Low MI, SonoVue → active disease
• Maximum peak intensity: 97%, 83% (sens, spec)
• Wash-in slope: 86%, 83%
• **Conclusion**: CEUS is a promising method for objective, assessment of disease activity in ileal CD

14 adults with acute exacerbation

CEUS performed at 0, 1, 3, 12 months

6/14 failed therapy
  - Significant differences in peak enhancement, wash-in slope, and area-under-wash-in phase at 1-month

**Conclusion**: CEUS perfusion analysis at 1-month can predict therapy efficacy

Saevik F, et al. *Inflamm Bowel Dis* 2014; 20:2029-2037
CEUS: Meta-Analysis

- 8 articles, 428 patients
- Pooled sensitivity: 93%
- Pooled specificity: 87%
- **Conclusion**: CEUS has high accuracy for detection of active CD using endoscopy/clinical indices as reference standards

CEUS: Phlegmon vs. Abscess

- 50 patients, 71 inflammatory masses at CEUS
  - $k = 0.97$ for abscess vs. phlegmon (gold std = other imaging modality, OR findings)
  - $k = 0.95$ interobserver agreement for abscess vs. phlegmon
  - Significant change in size pre-/post-contrast

- **Conclusion**: CEUS is an accurate method for distinguishing between intra-abdominal phlegmon and abscess, especially in CD

CEUS & Pediatric CD

Paucity of Data!
So, Can We Perform CEUS in Children for CD?

- Yes – but complicated
- Clinical use: “off-label”
- Systematic research: requires U.S. FDA “Investigational New Drug” application
What is an IND?

- Allows use of experimental drug for clinical research purposes
  - Includes “off-label” use of approved drug
  - Pertains to intravascular contrast agents
- Application reviewed by FDA to assure subjects not exposed to unreasonable risk
- If approved, research usually considered Phase I
So, What are We Doing?

1. Animal investigations:

- PE
- WIR
So, What are We Doing?

2. Preparing for pediatric CD research
   a. FDA IND – DONE
      • Optison: known small bowel CD, up to 3 injections
   b. Local IRB approval – DONE
University of Michigan Health System
Attention: Jonathan R. Dillman, M.D.
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Dear Dr. Dillman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Optison™, (Perflutren Protein-Type A Microspheres Injectable Suspension, USP).

We have completed our 30-day, safety review of your application and have concluded that you may proceed with your proposed clinical investigation to determine if Contrast-Enhanced Ultrasound (CEUS) using Optison can accurately discriminate and quantify bowel wall inflammation and fibrosis in human Crohn's Disease.
Conclusions

• Imaging plays critical role in diagnosis & follow-up of pediatric CD

• CEUS is likely viable imaging method for assessing CD inflammatory activity in children
  – Numerous benefits when compared to CT and MRI
  – Possible quantitative biomarker
  – Needs advocates, research

• IND process is doable